REMARKS

Claims 1-27 are currently pending in the application. Claims 26 and 27 have been withdrawn from consideration as being drawn to a non-elected invention. In view of the remarks below, Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the June 11, 2007 Office Action.

Rejection Under 35 USC § 102

Claims 1-16 and 18-25 have been rejected under 35 USC § 102(e) as allegedly being anticipated by United States Patent No. 6,277,875 (hereinafter "Holman"). According to the Office Action, Holman allegedly discloses a composition comprising pramipexole dihydrochloride monohydrate and several pharmaceutically-inert excipients in various dosage forms. For the reasons that follow, Applicants traverse this rejection and respectfully request that the rejection be withdrawn.

The present invention, as encompassed by the claims, is directed to a *sustained-release* pharmaceutical composition of pramipexole that exhibits: (a) an *in vitro* release profile wherein on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test; or (b) an *in vivo* pramipexole absorption profile following single dose oral administration to healthy adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours.

Anticipation requires the disclosure in a prior art reference of each and every limitation as set forth in the claim. As suggested in the Office Action, Holman discloses the use of MIRAPEX® — an *immediate release* pramipexole dosage form that needs to be administered three-times-a-day to patients suffering from CNS disorders. There is no disclosure in Holman of a sustained-release pramipexole composition having the claimed *in vitro* release profile of only 20% dissolution after 2 hours or the claimed *in vivo* absorption profile – following single dose administration – wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours. Accordingly, the presently claimed sustained-release compositions cannot be anticipated by Holman.

According to the Office Action, however, the release/absorption profile claimed by the present invention has not been given any patentable weight because it is alleged that the

MIRAPEX® tablets described in Holman are capable of performing the "intended use" (i.e., the sustained release / absorption profile) of the presently claimed invention. This, however, is not the case. Rather, as set forth in the pertinent sections of the Physician's Desk Reference (attached hereto), MIRAPEX® "is *rapidly* absorbed" and "reach[es] *peak* concentrations in approximately 2 hours." *See* Physicians Desk Reference 54^{th} Edition, at p. 2468 (emphasis added). Thus, contrary to the allegation in the Office Action, MIRAPEX® does not, and cannot, reach a pramipexole concentration of only about 20% after 2 hours (and only 40% after 4 hours) following administration. Consequently, it is respectfully submitted that the rejection should be withdrawn.

Rejection For Alleged Double Patenting

In addition, Claims 1-16, and 18-25 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over Claims 1-23 of co-pending Application Serial No. 10/626,166 ("the '166 Application"). Applicants respectfully traverse this rejection. More particularly, the claims of present application and those of the co-pending '166 Application are patentably distinct from each other. As set forth above, the claims of the present invention are directed to sustained-release pramipexole compositions that exhibit a particular "*in vitro* release profile" and "*in vivo* absorption profile." But, as stated in the Office Action, such claim limitations were not afforded any "patentable weight," and therefore, improperly ignored. The claims of the '166 Application are directed to particular pramipexole compositions that comprise, *inter alia*, a starch having a particular tensile strength. The claims of present application do not require the inclusion of the starch limitation; accordingly, contrary to the allegations contained in the Office Action, such claims are patentably distinct over those in the '166 Application. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection Under 35 USC § 103(a) Of Claims

Claim 17 has been rejected as allegedly being obvious under 35 U.S.C. §103(a) over Holman, discussed supra, in view of United States Patent No. 3,845,770 to Theeuwes et al. (hereinafter, "Theeuwes"). More particularly, the Office Action alleges that Theeuwes teaches the use of an osmotic pump to dispense a composition at a controlled rate.

In response, Applicants submit that a *prima facie* case of obviousness has not been established and respectfully request reconsideration and withdrawal of the rejection. To

establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references. Second, there must be a reasonable expectation of success. Third, the prior art, when combined, must teach or suggest all of the claim limitations.

In the present situation, it is respectfully submitted that the above criteria have not been established. First, there is no suggestion or motivation to combine the disclosure of Holman with that of Theeuwes. As discussed above, Holman discloses the use of MIRAPEX®, *orally*-administrable *immediate* release versions of pramipexole, for the treatment of fibromyalgia. Holman contains no teaching or suggestion, much less disclosure, of the need or desire for the sustained-release of pramipexole when treating fibromyalgia. Theeuwes, moreover, does not supply the missing teaching. Rather, Theeuwes discloses an osmotic drug delivery *device* for *insertion* into the eye: "[t]he novel osmotic drug delivery device of this invention is designed for insertion in the cul-de-sac of the conjunctiva between [the] sclera of [the] eyeball and upper eyelid . . . or [a] device . . . for positioning in the cul-de-sac of the conjunctiva between [the] sclera of [the] eyeball and lower eyelid, generally to be held in drug administration position by the natural pressure of the respective eyelid." (Theeuwes, Col. 7, lines 43-51). Thus, the very differences in the types of active agents described therein, their desired routes of administration, and their respective indications clearly suggest a *lack* of motivation to combine Theeuwes with Holman.

Nevertheless, even if some alleged motivation to combine the two references could be found in the prior art, the resulting combination would not – and could not – teach or suggest each of the claimed limitations of the present invention. As stated above, the prior art citations to MIRAPEX® do not teach or suggest the claimed sustained-release, once-daily pramipexole compositions, much less those having the particular *in vitro* release profile and *in vivo* absorption profile claimed herein. Rather, Holman suggests using an immediate-release pramipexole dosage form that needs to be administered three-times-a-day to patients suffering from CNS disorders to treat fibromyalgia. In this regard, neither reference teaches or suggests a pramipexole composition having: (a) an *in vitro* release profile wherein on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test; or (b) an *in vivo* pramipexole absorption profile following single dose oral administration to healthy adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than

about 4 hours. Indeed, the Office Action does not point to any particular disclosure in either of the cited references that would contradict this point.

Consequently, the rejection is based merely on the theory that a sustained-release dosage form of pramipexole could be obtained because technology to delay drug release – in particular, the osmotic delivery device of Theeuwes – is generally known in the art. That, however, is neither the standard for determining obviousness; nor is it accurate in the context of the present invention. The present invention enables the dosing of pramipexole – a highly-water soluble drug – to be reduced from three-times-a-day to once-a-day. Thus, the present invention provides the same overall drug exposure as MIRAPEX®, while reducing fluctuations between peak and trough blood drug concentrations. The reduced dosing facilitated by the present invention promotes patient compliance. Indeed, as set forth in the present application, "[t]he primary indication for [pramipexole], Parkinson's disease, is an affliction that becomes more prevalent with advancing age and is often accompanied by decline in memory. *See* Present Application at ¶ [0004]. Thus, "[a] once-daily regimen would be especially useful in enhancing compliance among elderly patients." *See id.*

Finally, the rejection ignores the well-established principle that the development of a sustained-release formulation for any particular drug is highly compound-specific. Thus, contrary to the allegation contained in the Office Action, methods of achieving the sustained release of one compound are not predictive of success with another compound possessing different chemical properties. Accordingly, one of ordinary skill in the art would find no motivation to combine or modify (or both) the teachings of the prior art to arrive at the claimed invention – particularly in view of the highly unique characteristics of pramipexole, which make it difficult to formulate it as a sustained-release dosage form. Indeed, as set forth in the present application, pramipexole is highly soluble in water (about 200 mg/ml at 225°C). Highly water-soluble drugs, such as those with a solubility of about 10 mg/ml or greater, present challenges to the formulator wishing to provide a sustained-release dosage form, and the higher the solubility the greater are the challenges. These challenges are well illustrated in the case of pramipexole "because of the tendency of the drug to rapidly leach out of the dosage form upon exposure to an aqueous medium, such as gastrointestinal fluid." *See* Present Application at ¶ [0025]. Because the teachings of the cited references provide no guidance regarding how to formulate a highly water soluble drug, such as pramipexole, into a sustained-release dosage form, the citations cannot render the claimed invention obvious. Accordingly, it is respectfully requested that the rejection of claim 17 as allegedly obvious over Holman in view of Theeuwes be withdrawn.

Conclusion

In view of the remarks above, Applicants respectfully submit that the pending claims are fully allowable, and solicit the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicants' undersigned attorneys at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required or to credit any overpayment to Deposit Account No. 16-1445.

Respectfully submitted,

Dated: December 7, 2007

John C. Martin
Reg. No. 42,843

Pfizer Inc.
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212) 733-0538

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tion should be treated with insulin [illegible]

3. Type I diabetes mellitus, as [illegible]

SPECIAL WARNING ON INCREASED RISK OF CAR-DIOVASCULAR MORTALITY

The administration of oral hypoglycemic [illegible] reported to be associated with increased [illegible] mortality as compared to treatment with [illegible] plus insulin. This warning is based on the [illegible] by the University Group Diabetes Program [illegible] term prospective clinical trial designed to [illegible] fectiveness of glucose-lowering drugs in [illegible] laying vascular complications in patients [illegible] dependent diabetes. The study involved [illegible] were randomly assigned to one of four [illegible] (*Diabetes*, 19 (Suppl. 2):747-830, 1970)

UGDP reported that patients treated for [illegible] diet plus a fixed dose of tolbutamide [illegible] had a rate of cardiovascular mortality [illegible] times that of patients treated with diet alone [illegible] increase in total mortality was not observed [illegible] tolbutamide was discontinued based on the [illegible] diovascular mortality, thus limiting the [illegible] study to show an increase in overall mortality [illegible] troversy regarding the interpretation of these [illegible] findings of the UGDP study provide an [illegible] this warning. The patient should be informed [illegible] tial risks and advantages of MICRONASE and [illegible] modes of therapy.

Although only one drug in the sulfonylurea [illegible] mide) was included in this study, it is prudent [illegible] standpoint to consider that this warning may [illegible] other oral hypoglycemic drugs in this class [illegible] close similarities in mode of action and chemical [illegible]

PRECAUTIONS

General

Hypoglycemia: All sulfonylureas are capable [illegible] severe hypoglycemia. Proper patient selection [illegible] and instructions are important to avoid hypoglycemic [illegible] sodes. Renal or hepatic insufficiency [illegible] drug levels of glyburide and the latter [illegible] gluconeogenic capacity, both of which [illegible] rious hypoglycemic reactions. Elderly, debilitated [illegible] nourished patients, and those with adrenal [illegible] sufficiency, are particularly susceptible to the [illegible] action of glucose-lowering drugs. Hypoglycemia [illegible] ficult to recognize in the elderly and in people [illegible] ing beta-adrenergic blocking drugs. Hypoglycemia [illegible] likely to occur when caloric intake is deficient [illegible] or prolonged exercise, when alcohol is [illegible] more than one glucose lowering drug [illegible] hypoglycemia may be increased with [illegible]

Loss of Control of Blood Glucose: When [illegible] lized on any diabetic regimen is exposed to [illegible] fever, trauma, infection or surgery, a loss [illegible] cur. At such times it may be necessary to [illegible] MICRONASE and administer insulin.

The effectiveness of any hypoglycemic [illegible] MICRONASE, in lowering blood glucose to [illegible] decreases in many patients over a period of time [illegible] be due to progression of the severity of diabetes [illegible] ished responsiveness to the drug. This [illegible] known as secondary failure, to distinguish it from [illegible] failure in which the drug is ineffective in an [illegible] tient when MICRONASE is first given. Adequate [illegible] ment of dose and adherence to diet should be [illegible] fore classifying a patient as a secondary failure.

Information for Patients: Patients should be [illegible] the potential risks and advantages of MICRONASE [illegible] alternative modes of therapy. They also should [illegible] about the importance of adherence to dietary [illegible] of a regular exercise program, and of regular [illegible] urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and [illegible] and conditions that predispose to its development [illegible] explained to patients and responsible family [illegible] mary and secondary failure also should be explained.

Laboratory Tests

Therapeutic response to MICRONASE Tablets [illegible] monitored by frequent urine glucose tests and [illegible] glucose tests. Measurement of glycosylated hemoglobin [illegible] els may be helpful in some patients.

Drug Interactions

The hypoglycemic action of sulfonylureas may be [illegible] ated by certain drugs including nonsteroidal anti-inflamma[illegible] tory agents and other drugs that are highly protein [illegible] salicylates, sulfonamides, chloramphenicol, probenecid [illegible] marins, monoamine oxidase inhibitors, and beta [illegible] blocking agents. When such drugs are administered [illegible] tient receiving MICRONASE, the patient should [illegible] served closely for hypoglycemia. When such drugs [illegible] drawn from a patient receiving MICRONASE, the [illegible] should be observed closely for loss of control.

Certain drugs tend to produce hyperglycemia and [illegible] to loss of control. These drugs include the thiazides [illegible] other diuretics, corticosteroids, phenothiazines [illegible] products, estrogens, oral contraceptives, phenytoin [illegible] tinic acid, sympathomimetics, calcium channel [illegible] drugs, and isoniazid. When such drugs are administered [illegible] a patient receiving MICRONASE, the patient should [illegible] closely observed for loss of control. When such [illegible] withdrawn from a patient receiving MICRONASE [illegible] tient should be observed closely for hypoglycemia.

[illegible] has been reported [illegible] [illegible] glycemic action of glyburide. The [illegible] tion is not known. [illegible] between oral miconazole and oral [illegible] ing to severe hypoglycemia has [illegible] this interaction also occurs with the [illegible] ginal preparations of miconazole [illegible]

[illegible] dose interaction study in NIDDM [illegible] glyburide AUC and C_{max} were ob[illegible] variable. The single-dose nature of [illegible] of correlation between glyburide [illegible] dynamic effects, makes the clini[illegible] interaction uncertain. Coadministra[illegible] metformin did not result in any [illegible] min pharmacokinetics or pharma[illegible]

[illegible] genesis, and Impairment of Fertility

[illegible] up to 300 mg/kg/day for 18 months [illegible] effects. Glyburide is nonmutagenic [illegible] monella microsome test (Ames test) [illegible] alkaline elution assay. No drug re[illegible] in any of the criteria evaluated in [illegible] study of glyburide in mice.

[illegible] Pregnancy Category B

[illegible] have been performed in rats and rab[illegible] times the human dose and have re[illegible] impaired fertility or harm to the fetus [illegible] are, however, no adequate and well [illegible] pregnant women. Because animal re[illegible] not always predictive of human re[illegible] should be used during pregnancy only if [illegible]

[illegible] mation suggests that abnormal blood [illegible] pregnancy are associated with a [illegible] congenital abnormalities, many experts [illegible] be used during pregnancy to main[illegible] close to normal as possible.

[illegible] Effects: Prolonged severe hypoglycemia [illegible] reported in neonates born to mothers [illegible] sulfonylurea drug at the time of deliv[illegible] reported more frequently with the use of [illegible] half-lives. If MICRONASE is used [illegible] should be discontinued at least two [illegible] expected delivery date.

[illegible] known whether glyburide is excreted in [illegible] sulfonylurea drugs are known to be ex[illegible]. Because the potential for hypoglyce[illegible] may exist, a decision should be made [illegible] nursing or to discontinue the drug, [illegible] the importance of the drug to the [illegible] discontinued, and if diet alone is in[illegible] controlling blood glucose, insulin therapy [illegible]

[illegible] ness in pediatric patients have not been [illegible]

[illegible] ACTIONS

[illegible] Precautions and Overdosage Sections.

[illegible] **Reactions:** Cholestatic jaundice and hep[illegible] rarely; MICRONASE Tablets should be dis[illegible] occurs. [illegible] abnormalities, including isolated transami[illegible] have been reported. [illegible] disturbances, eg, nausea, epigastric full[illegible] are the most common reactions, having [illegible] of treated patients during clinical trials. [illegible] dose related and may disappear when dos[illegible]

[illegible] **Reactions:** Allergic skin reactions, *eg*, pruri[illegible] urticaria, and morbilliform or maculopap[illegible] occurred in 1.5% of treated patients during [illegible] these may be transient and may disappear [illegible] use of MICRONASE; if skin reactions [illegible] should be discontinued. [illegible] tarda and photosensitivity reactions [illegible] with sulfonylureas.

[illegible] **Reactions:** Leukopenia, agranulocytosis, [illegible] hemolytic anemia, aplastic anemia, and [illegible] have been reported with sulfonylureas.

[illegible] **Reactions:** Hepatic porphyria and disulfiram[illegible] have been reported with sulfonylureas; [illegible] porphyria has not been reported with [illegible] and disulfiram-like reactions have been re[illegible] rarely.

[illegible] natremia have been reported with glyburide [illegible] sulfonylureas, most often in patients who are [illegible] tions or have medical conditions known to [illegible] emia or increase release of antidiuretic hor[illegible] syndrome of inappropriate antidiuretic hormone [illegible] tion has been reported with certain other sul[illegible] and it has been suggested that these sulfonylu[illegible] ment the peripheral (antidiuretic) action of [illegible] increase release of ADH.

[illegible] **tions:** Changes in accommodation and/or [illegible] have been reported with glyburide and other [illegible] These are through to be related to fluctuation [illegible]

[illegible] dermatologic reactions, allergic reactions [illegible] edema, arthralgia, myalgia and vasculitis [illegible] ported.

[illegible] lets, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate which will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with MICRONASE Tablets or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, *ie*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *ie*, loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of MICRONASE may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

Usual Starting Dose

The usual starting dose of MICRONASE Tablets is 2.5 to 5 mg daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1.25 mg daily. (See PRECAUTIONS section for patients at increased risk.) Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Transfer From Other Hypoglycemic Therapy Patients Receiving Other Oral Antidiabetic Therapy: Transfer of patients from other oral antidiabetic regimens to MICRONASE should be done conservatively and the initial daily dose should be 2.5 to 5 mg. When transferring patients from oral hypoglycemic agents other than chlorpropamide to MICRONASE, no transition period and no initial or priming does are necessary. When transferring patients from chlorpropamide, particular care should be exercised during the first two weeks because the prolonged retention of chlorpropamide in the body and subsequent overlapping drug effects may provoke hypoglycemia.

Patients Receiving Insulin: Some Type II diabetic patients being treated with insulin may respond satisfactorily to MICRONASE. If the insulin dose is less than 20 units daily, substitution of MICRONASE Tablets 2.5 to 5 mg as a single daily dose may be tried. If the insulin dose is between 20 and 40 units daily, the patient may be placed directly on MICRONASE Tablets 5 mg daily as a single dose. If the insulin dose is more than 40 units daily, a transition period is required for conversion to MICRONASE. In these patients, insulin dosage is decreased by 50% and MICRONASE Tablets 5 mg daily is started. Please refer to Titration to Maintenance Dose for further explanation.

Titration to Maintenance Dose

The usual maintenance dose is in the range of 1.25 to 20 mg daily, which may be given as a single dose or in divided doses (See Dosage Interval section). Dosage increases should be made in increments of no more than 2.5 mg at weekly intervals based upon the patient's blood glucose response.

No exact dosage relationship exists between MICRONASE and the other oral hypoglycemic agents. Although patients may be transferred from the maximum dose of other sulfonylureas, the maximum starting dose of 5 mg of MICRONASE Tablets should be observed. A maintenance dose of 5 mg of MICRONASE Tablets provides approximately the same degree of blood glucose control as 250 to 375 mg chlorpropamide, 250 to 375 mg tolazamide, 500 to 750 mg acetohexamide, or 1000 to 15 00 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of MICRONASE Tablets 5 mg concomitantly with a 50% reduction in insulin dose. Progressive withdrawal of insulin and increase of MICRONASE in increments of 1.25 to 2.5 mg every 2 to 10 days is then carried out. During this conversion period when both insulin and MICRONASE are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least three times daily and report results to their physician. The appearance of persistent acetonuria with glycosuria indicates that the patient is a Type I diabetic who requires insulin therapy.

Concomitant Glyburide and Metformin Therapy

MICRONASE Tablets should be added gradually to the dosing regimen of patients who have not responded to the maximum dose of metformin monotherapy after four weeks (see Usual Starting Dose and Titration to Maintenance Dose). Refer to metformin package insert.

identify the optimal dose of each drug needed to achieve [illegible] goal. With concomitant glyburide and metformin therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (see PRECAUTIONS section).

Maximum Dose

Daily doses of more than 20 mg are not recommended.

Dosage Interval

Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

Specific Patient Populations

MICRONASE is not recommended for use in pregnancy or for use in pediatric patients.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypolgycemic reactions. (See PRECAUTIONS section.)

HOW SUPPLIED

MICRONASE Tablets are supplied as follows:

MICRONASE Tablets 1.25 mg (White, Round, Scored, imprinted MICRONASE 1.25)

Bottles of 100	NDC 0009-0131-01

MICRONASE Tablets 2.5 mg (Dark Pink, Round, Scored, imprinted MICRONASE 2.5)

Bottles of 100	NDC 0009-0141-01
Bottles of 1000	NDC 0009-1041-03
Unit Dose Pkg of 100	NDC 0009-0141-02

MICRONASE Tablets 5 mg (Blue, Round, Scored imprinted MICRONASE 5)

Bottles of 30	NDC 0009-0171-11
Bottles of 60	NDC 0009-0171-12
Bottles of 100	NDC 0009-0171-05
Bottles of 500	NDC 0009-0171-06
Bottles of 1000	NDC 0009-0171-07
Unit Dose Pkg of 100	NDC 0009-0171-03

Rx only

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]. Dispensed in well closed containers with safety closures. Keep container tightly closed.

Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
Revised February 1999 811 985 722
692166

MIRAPEX® ℞

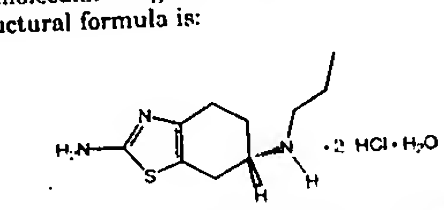
[*mīr-ă-pex*]

pramipexole
dihydrochloride tablets

DESCRIPTION

MIRAPEX Tablets contain pramipexole, a dopamine agonist indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease. The chemical name of pramipexole dihydrochloride is (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate. Its empirical formula is $C_{10}H_{17}N_3S \cdot 2\ HCl \cdot H_2O$, and its molecular weight is 302.27.

The structural formula is:



Pramipexole dihydrochloride is a white to off-white powder substance. Melting occurs in the range of 296° C to 301° C, with decomposition. Pramipexole dihydrochloride is more than 20% soluble in water, about 8% in methanol, about 0.5% in ethanol, and practically insoluble in dichloromethane.

MIRAPEX Tablets, for oral administration, contain 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, or 1.5 mg of pramipexole dihydrochloride monohydrate. Inactive ingredients consist of mannitol, corn starch, colloidal silicon dioxide, povidone, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pramipexole is a nonergot dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D_2 subfamily of dopamine receptors, binding with higher affinity to D_3 than to D_2 or D_4 receptor subtypes. The relevance of D_3 receptor binding in Parkinson's disease is unknown.

The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiologic studies in animals that have demon-

Continued on next page

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Mirapex—Cont.

strated that pramipexole influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum.

Pharmacokinetics

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of pramipexole absorption, although the time of maximum plasma concentration (T_{max}) is increased by about 1 hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation [CV]=20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.

Pramipexole displays linear pharmacokinetics over the clinical dosage range. Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations.) Steady-state concentrations are achieved within 2 days of dosing.

Metabolism and elimination: Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. Nonrenal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. The renal clearance of pramipexole is approximately 400 mL/min (CV=25%), approximately three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.

Pharmacokinetics In Special Populations

Because therapy with pramipexole is initiated at a subtherapeutic dosage and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, or age is not necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see CLINICAL PHARMACOLOGY, Renal Insufficiency).

Gender: Pramipexole clearance is about 30% lower in women than in men, but most of this difference can be accounted for by differences in body weight. There is no difference in half-life between males and females.

Age: Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower, respectively, in elderly (aged 65 years or older) compared with young healthy volunteers (aged less than 40 years). This difference is most likely due to the well-known reduction in renal function with age, since pramipexole clearance is correlated with renal function, as measured by creatinine clearance (see CLINICAL PHARMACOLOGY, Renal Insufficiency).

Parkinson's disease patients: A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's disease patients compared with healthy elderly volunteers. The reason for this difference appears to be reduced renal function in Parkinson's disease patients, which may be related to their poorer general health. The pharmacokinetics of pramipexole were comparable between early and advanced Parkinson's disease patients.

Pediatric: The pharmacokinetics of pramipexole in the pediatric population have not been evaluated.

Hepatic insufficiency: The influence of hepatic insufficiency on pramipexole pharmacokinetics have not been evaluated. Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on pramipexole elimination.

Renal insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment (creatinine clearance approximately 20 mL/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/min) compared with healthy volunteers. A lower starting and maintenance dose is recommended in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis. Caution should be exercised when administering pramipexole to patients with renal disease.

CLINICAL STUDIES

The effectiveness of MIRAPEX Tablets in the treatment of Parkinson's disease was evaluated in a multinational drug development program of seven randomized, controlled trials. Three were conducted in patients with early Parkinson's disease who were not receiving concomitant levodopa, and four were conducted in patients with advanced Parkinson's disease who were receiving concomitant levodopa. Among these seven studies, three studies provide the most persuasive evidence of pramipexole's effectiveness in the management of patients with Parkinson's disease who were and were not receiving concomitant levodopa. Two of these three trials enrolled patients with early Parkinson's disease (not receiving levodopa), and one enrolled patients with advanced Parkinson's disease who were receiving maximally tolerated doses of levodopa.

In all studies, the Unified Parkinson's Disease Rating Scale (UPDRS), or one or more of its subparts, served as the primary outcome assessment measure. The UPDRS is a four-part multi-item rating scale intended to evaluate mentation (part I), activities of daily living (part II), motor performance (part III), and complications of therapy (part IV).

Part II of the UPDRS contains 13 questions relating to activities of daily living (ADL), which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items) and is scored as described for part II. It is designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (eg, tremor, rigidity, bradykinesia), postural instability, etc), scored for different body regions, and has a maximum (worst) score of 108.

Studies in Patients With Early Parkinson's Disease

Patients (N=599) in the two studies of early Parkinson's disease had a mean disease duration of 2 years, limited or no prior exposure to levodopa (generally none in the preceding 6 months), and were not experiencing the "on-off" phenomenon and dyskinesia characteristic of later stages of the disease.

One of the two early Parkinson's disease studies (N=335) was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients could be on selegiline, anticholinergics, or both, but could not be on levodopa products or amantadine. Patients were randomized to MIRAPEX or placebo. Patients treated with MIRAPEX had a starting daily dose of 0.375 mg and were titrated to maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At the end of the 6-month maintenance period, the mean improvement from baseline on the UPDRS part II (ADL) total score was 1.9 in the group receiving MIRAPEX and -0.4 in the placebo group, a difference that a was statistically significant. The mean improvement from baseline on the UPDRS part III total score was 5.0 in the group receiving MIRAPEX and -0.8 in the placebo group, a difference that was also statistically significant. A statistically significant difference between groups in favor of MIRAPEX was seen beginning at week 2 of the UPDRS part II (maximum dose 0.75 mg/day) and at week 3 of the UPDRS part III (maximum dose 1.5 mg/day).

The second early Parkinson's disease study (N=264) was a double-blind, placebo-controlled, parallel trial consisting of a 6-week dose-escalation period a 4-week maintenance period. Patients could be on selegiline, anticholinergics, amantadine, or any combination of these, but could not be on levodopa products. Patients were randomized to 1 of 4 fixed doses of MIRAPEX (1.5 mg 3.0 mg, 4.5 mg, or 6.0 mg per day) or placebo. At the end of the 4-week maintenance period, the mean improvement from baseline on the UPDRS part II total score was 1.8 in the patients treated with MIRAPEX, regardless of assigned dose group, and 0.3 in placebo-treated patients. The mean improvement from baseline on the UPDRS part III total score was 4.2 in patients treated with MIRAPEX and 0.6 in placebo-treated patients. No dose-response relationship was demonstrated. The between-treatment differences on both parts of the UPDRS were statistically significant in favor of MIRAPEX for all doses.

No differences in effectiveness based on age or gender were detected. There were too few non-Caucasian patients to evaluate the effect of race. Patients receiving selegiline or anticholinergics had responses similar to patients not receiving these drugs.

Studies in Patients With Advanced Parkinson's Disease

In the advanced Parkinson's disease study, the primary assessments were the UPDRS and daily diaries that quantified amounts of "on" and "off" time.

Patients in the advanced Parkinson's disease study (N=360) had a mean disease duration of 9 years, had been exposed to levodopa for long periods of time (mean 8 years), used concomitant levodopa during the trial, and had "on-off" periods. The advanced Parkinson's disease study was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients were all treated with concomitant levodopa products and could additionally be on concomitant selegiline, anticholinergics, amantadine, or any combination. Patients treated with MIRAPEX had a starting dose of 0.375 mg/day and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At selected times during the 6-month maintenance period, patients were asked to record the amount of "off," "on," or "on with dyskinesia" time per day for several sequential days. At the end of the 6-month maintenance period, the mean improvement from baseline on the UPDRS part II total score was 2.7 in the group treated with MIRAPEX and 0.5 in the placebo group, a difference that was statistically significant. The mean improvement from baseline on the UPDRS part III total score was 5.6 in the group treated with MIRAPEX and 2.8 in the placebo group, a difference that was statistically significant. A statistically significant difference between groups in favor of MIRAPEX was seen at week 3 of the UPDRS part II (maximum dose 1.5 mg/day) and at week 2 of the UPDRS part III (maximum dose 0.75 mg/day). Dosage reduction of levodopa was allowed during this study if dyskinesia (or hallucinations) developed; levodopa dosage reduction occurred in 76% of patients treated with MIRAPEX versus 54% of placebo patients. On average, the levodopa dose was reduced 27%.

The mean number of "off" hours per day during ... was 6 hours for both treatment groups. Through... trial, patients treated with MIRAPEX had a mean ... hours per day, while placebo-treated patients cont... experience 6 "off" hours per day.

No differences in effectiveness based on age or gen... detected. There were too few non-Caucasian pat... evaluate the effect of race.

INDICATIONS AND USAGE

MIRAPEX Tablets are indicated for the treatm... signs and symptoms of idiopathic Parkinson's di... The effectiveness of MIRAPEX was demonstrat... domized, controlled trials in patients with early P... disease who were not receiving concomitant levod... apy as well as in patients with advanced disease o... itant levodopa (see CLINICAL STUDIES).

CONTRAINDICATIONS

MIRAPEX Tablets are contraindicated in patient... demonstrated hypersensitivity to the drug or it... ents.

WARNINGS

Symptomatic Hypotension: Dopamine agonists... studies and clinical experience, appear to imp... temic regulation of blood pressure, with result... static hypotension, especially during dose escal... kinson's disease patients, in addition, appear to b... paired capacity to respond to an orthostatic ch... these reasons, Parkinson's disease patients b... with dopaminergic agonists ordinarily require ... itoring for signs and symptoms of orthostatic h... especially during dose escalation, and should b... this risk (see PRECAUTIONS, Information for...

In clinical trials for pramipexole, however, and ... orthostatic effects in normal volunteers, the ... dence of clinically significant orthostatic hyp... not greater among those assigned to MIRAP... than among those assigned to placebo. This re... unexpected in light of the previous experience... of dopamine agonist therapy.

While this finding could reflect a unique prop... pexole, it might also be explained by the co... study and the nature of the population enrol... ical trials. Patients were very carefully tit... tients with active cardiovascular disease or ... thostatic hypotension at baseline were excl...

Hallucinations: In the three double-blin... trolled trials in early Parkinson's disease... were observed in 9% (35 of 388) of pat... MIRAPEX, compared with 2.6% (6 of 235) ... ing placebo. In the four double-blind, place... als in advanced Parkinson's disease, wh... ceived MIRAPEX and concomitant levodop... were observed in 16.5% (43 of 260) of pa... MIRAPEX compared with 3.8% (10 of 2... ceiving placebo. Hallucinations were of su... cause discontinuation of treatment in 3 1... kinson's disease patients and 2.7% of the ... son's disease patients compared with ab... patients in both populations.

Age appears to increase the risk of hall... able to pramipexole. In the early Park... tients, the risk of hallucinations was 1.9... placebo in patients younger than 65 ... greater than placebo in patients older t... advanced Parkinson's disease patients... nations was 3.5 times greater than ... younger than 65 years and 5.2 times gr... patients older than 65 years.

PRECAUTIONS

Rhabdomyolysis: A single case of ... curred in a 49-year-old male with adv... ease treated with MIRAPEX Tablets... pitalized with an elevated CPK (10,... toms resolved with discontinuation o...

Renal: Since pramipexole through ... should be exercised when prescribin... with renal insufficiency (see DOSAG... TION).

Dyskinesia: MIRAPEX may pote... side effects of levodopa and may ca... isting dyskinesia. Decreasing the do... liorate this side effect.

Retinal pathology in albino rats: ... generation and loss of photorecept... the retina of albino rats in the 2-... Evaluation of the retinas of alb... monkeys, and minipigs did not re... potential significance of this effe... established, but cannot be disreg... mechanism that is universally ... disk shedding) may be involved ... GY).

Events Reported With Dopamin...

Although the events enumerat... ported in association with the ... velopment program, they are ... other dopaminergic drugs. The ... events, however, is so low that ... these events at rates similar to ... dopaminergic therapies, it wo... single case would have occurr... posed to pramipexole in stud...

...***awal-emergent hyperpyrexia and confusion:*** Al... not reported with pramipexole in the clinical devel... program, a symptom complex resembling the neu... malignant syndrome (characterized by elevated ...ature, muscular rigidity, altered consciousness, and ...ic instability), with no other obvious etiology, has ...ported in association with rapid dose reduction, ...al of, or changes in antiparkinsonian therapy.

...***complications:*** Although not reported with prami... in the clinical development program, cases of retro... fibrosis, pulmonary infiltrates, pleural effusion, ...ural thickening have been reported in some patients ... with ergot-derived dopaminergic agents. While ...plications may resolve when the drug is discontin... ...plete resolution does not always occur.

... these adverse events are believed to be related to ...line structure of these compounds, whether other, ... derived dopamine agonists can cause them is un...

...**on for Patients:** Patients should be instructed to ...APEX only as prescribed.

... should be informed that hallucinations can occur ... the elderly are at a higher risk than younger pa... ...h Parkinson's disease.

... may develop postural (orthostatic) hypotension, ...ithout symptoms such as dizziness, nausea, faint... ...ckouts, and sometimes, sweating. Hypotension ... more frequently during initial therapy. Accord... ...nts should be cautioned against rising rapidly af... or lying down, especially if they have been doing ...nged periods and especially at the initiation of ... with MIRAPEX.

...hould be advised that MIRAPEX may cause som... that they should neither drive a car nor operate ...lax machinery until they have gained sufficient ...m MIRAPEX to gauge whether or not it affects ...l and/or motor performance adversely. Because ...le additive sedative effects, caution should also ... patients are taking other CNS depressants in ... with MIRAPEX.

... teratogenic potential of pramipexole has not ...ely established in laboratory animals, and be...nce in humans is limited, patients should be ...otify their physicians if they become pregnant ...become pregnant during therapy (see PRECAU... ...nancy).

... possibility that pramipexole may be excreted ..., patients should be advised to notify their ...they intend to breast-feed or are breast-feeding

...velop nausea, they should be advised that tak... ... with food may reduce the occurrence of nau...

...**ts:** During the development of MIRAPEX, ... abnormalities on routine laboratory testing ...therefore, no specific guidance is offered re... ... monitoring; the practitioner retains respon... ...rmining how best to monitor the patient in

...***odopa:*** Carbidopa/levodopa did not influ... ...cokinetics of pramipexole in healthy volun... ...amipexole did not alter the extent of absorp... the elimination of carbidopa/levodopa, al... an increase in levodopa C_{max} by about 40% ... in T_{max} from 2.5 to 0.5 hours.

...healthy volunteers (N=11), selegiline did not ...rmacokinetics of pramipexole.

...opulation pharmacokinetic analysis sug... ...adine is unlikely to alter the oral clearance ...(N=54).

...tidine, a known inhibitor of renal tubu... ...ganic bases via the cationic transport sys... ... increase in pramipexole AUC and a 40% ... (N=12).

...benecid, a known inhibitor of renal tubu... ...anic acids via the anionic transporter, did ...fluence pramipexole pharmacokinetics

...***nated via renal secretion:*** Population ...analysis suggests that coadministration of ...eted by the cationic transport system (eg, ...ine, diltiazem, triamterene, verapamil, ...nine) decreases the oral clearance of ...ut 20%, while those secreted by the an...tem (eg, cephalosporins, penicillins, indo... ...rothiazide, and chlorpropamide) are ... effect on the oral clearance of pramipex...

... Inhibitors of cytochrome P450 enzymes ...ed to affect pramipexole elimination be... ... not appreciably metabolized by these ... in vitro. Pramipexole does not inhibit ...1A2, CYP2C9, CY2C19, CYP2E1, and ... of CYP2D6 was observed with an ap... ...indicating that pramipexole will not in... ...at plasma concentrations observed fol... ...commended clinical dose (1.5 mg tid).

...**ts:** Since pramipexole is a dopamine ... that dopamine antagonists, such as ...nothiazines, butyrophenones, thioxan... ...amide, may diminish the effectiveness

...**Interactions:** There are no known ... MIRAPEX and laboratory tests.

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